CMC REVIEW

BLA 125197

Sipuleucel-T (Provenge®)

Dendreon Corporation

Division of Cell and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies

Reviewed by:

Keith Wonnacott, Ph.D.	_____	_____
Malcolm Moos Jr., M.D., Ph.D.	_____	_____
Syed Husain, Ph.D.	_____	_____
Thomas Finn, Ph.D.	_____	_____
	Signature	**Date**

Concurred by:

Kimberly Benton, Ph.D., **Deputy Division Director**	_____	_____
Raj Puri, M.D., Ph.D., **Division Director**	_____	_____
	Signature	**Date**

EXECUTIVE SUMMARY

Recommendation: Based on our review of Dendreon's BLA for sipuleucel-T, we have determined that several product manufacturing and control items need to be resolved before assurance of safety, identity, purity, and potency of the product is reached. Though the majority of the cellular component, and especially the recombinant protein component, of sipuleucel-T is manufactured to high standards, some questions remain regarding validation of assays and product stability and quality. These critical review issues are raised in the executive summary and discussed in more detail in the product review. They have also been included as letter comments at the end of this executive summary.

Product Overview:
[Sipuleucel-T]
Sipuleucel-T (Provenge™, APC8015) is a patient-specific autologous cellular therapy for the treatment of hormone refractory prostate cancer. The active ingredient of the product is antigen presenting cells that present a prostate cancer antigen, prostatic acid phosphatase, to the immune system. To manufacture sipuleucel-T, a patient's cells are collected by apheresis. Red blood cells and granulocytes are -b(4)-from the apheresis product by two buoyant density gradient separations, retaining the populations of leukocytes. PA2024, which consists of the prostatic acid phosphatase (PAP) linked to GM-CSF, is then added to the cells. The GM-CSF portion of the protein helps to target the PAP protein to antigen presenting cells and activate those cells. The PAP provides the tumor specific antigen that will direct the immune system to target prostate cancer. The cells are cultured in the presence of PA2024 for 36-44 hours. After culture, the cells are washed and suspended in lactated ringer's solution for infusion back into the patient.

The proposed mechanism of action of the product is that antigen presenting cells (APC) in the product will become activated and present the PAP antigen to T cells in the patient which can then target and kill cancer cells. Potency is measured as the number of cells expressing and the upregulation of the costimulatory molecule CD54. As measured by Dendreon, CD54 is expressed by the APC responsible for taking up PA2024 in ----b(4)----------

The course of therapy is 3 doses, given at approximately 2 week intervals. Each apheresis produces one dose of product, therefore the patient undergoes 3 separate apheresis procedures. Each apheresis product goes through the identical manufacturing process and is considered a unique lot of product. If a lot of product fails to meet requirements for quality, the patient must undergo an additional apheresis to make a new lot of product. Each dose is shipped and administered fresh (without cryopreservation) within 18 hours of manufacture. The lot release testing is performed simultaneous to product shipping. All lot release tests must meet specifications for the product to be infused and that information is faxed to the infusion site.

[PA2024]
PA2024 is a fusion protein consisting of human prostatic acid phosphatase (PAP) fused via a -b(4)---------- to Granulocyte-Macrophage Colony Stimulating factor (GM-CSF). PAP is expressed in prostate tissue, functioning in the context of this proposed therapy as a tumor-

associated antigen in patients with prostate cancer. GM-CSF is an immunostimulatory molecule. The fusion protein is added to immune cells obtained from each patient (see review for Sipuleucel-T) to stimulate anti-tumor activity.

The protein is ----b(4)---------- substance is shipped to a filling facility and filled using standard techniques.

Review findings:
[Sipuleucel-T]
One of the key criteria in evaluating CMC manufacturing data is to examine whether the manufacturer is able to make the product in a way that ensures product consistency, such that with reasonable assurance that the therapy established as safe and efficacious under phase III trials is the same as what will be delivered under licensure. Sipuleucel-T is generated from a leukapheresis which is inherently variable from patient to patient and lot to lot. The manufacturing protocol is not designed to reduce this variability. As a consequence, lot release specifications are set very wide. The variability of the product entails not only large differences in the number of cells, but the cellular composition, and the level of activation of the monocytes. Despite this variability, Dendreon has shown that sipuleucel-T product parameters have been consistent across two completed phase III studies and two ongoing phase III trials. Based upon this observation, and the fact that the manufacturing procedure is relatively straightforward, there is assurance that Dendreon can continue to manufacture this product to the standards outlined in the BLA. Recommendations were made to Dendreon in the CR letter comments suggesting ways in which the sponsor might reduce variability in cell number and potency. Comments were also included in the 483 inspection discussion items to include measuring other cell populations for the purposes of monitoring product quality.

Dendreon has chosen CD54 as a measure for potency and as a marker for the active component of the therapy. CD54 is not considered an APC marker and CD54 upregulation is not specific to monocytes. Nevertheless, Dendreon has demonstrated that the biological activity is present in the $CD54^{+}$ fraction, and that upregulation of CD54 on the monocyte-rich population correlates with improved survival in the treatment arm.

While the clinical manufacturing experience shows that overall this product can be consistently manufactured, it is questionable whether the actual manufacturing specifications ensure either a potent dose (individual lot/infusion) or a potent therapy (3 lots/infusions) will be given to all patients. This is not always easy to establish for cellular therapies considering the challenges in developing appropriate potency assays. Further, not all patients will respond to any therapy, including autologous cellular therapies. The lot release specifications for sipuleucel-T are based on 3 standard deviations from the mean of their manufacturing experience. This should allow approximately 97% of future lots to meet lot release criteria. The specifications for potency and cell number are as robust or more robust than used under phase III trials, with the exception of monitoring product composition. However, neither product development, nor clinical experience

support that the specifications set are truly meaningful. The scientific literature generally supports the idea that monocytes with this level of CD54 upregulation can be considered activated. Whether the level of activation is what is needed to effect a meaningful immune response is unclear.

In the absence of supportive product development data specifically addressing this question, the best source of information comes from the quartile analysis correlating CD54 upregulation with survival. While these data lend support to the use of CD54 as a measure of potency, it also suggests that patients in the lowest quartile had little benefit beyond placebo. A quartile analysis of all lots listed in the BLA shows that the lowest quartile on average did not display the increased upregulation seen in the 2nd and 3rd infusions compared to the 1st infusion, as observed in the other quartiles. Whether this represents a population of patients that received unpotent product, or represents patients incapable of significantly responding to this therapy cannot be distinguished at this time. Questions surrounding the CD54 upregulation lot release criteria are confounded by a lack of a clear clinical correlation of survival with the number or type of cells a patient receives.

Several issues were uncovered for the validation of some of the lot release assays. Of all the validation studies, the weakest support is for equivalency testing for the alternate sterility test method, and for stability and product shipping. Overall, Dendreon conducted a fairly comprehensive evaluation of the --b(4)---------- system used in place of the CFR/b(4) method. Where these studies fall short is in the head to head comparison between the two methods. Additional information provided by Dendreon in response to this concern, help support, but do not completely address this regulatory issue. A letter comment covering this issue asks for clarification on the comparison studies performed, including studies conducted using the -b(4)---------- system that is present in their Seattle manufacturing facility. Also requested is more information on the additional studies Dendreon stated in the BLA they will conduct to "further demonstrate that suitability of the ---b(4)----------
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From a product quality standpoint, the more relevant issue is the shipping validation studies. Studies conducted to validate the shipping container and the stability of the cells throughout the proposed 18 hour shelf life may not be sufficiently robust. Also of concern was the lack of data from cells manufactured and shipped from the New Jersey facility, and limited use of temperature probes in establishing that the shipping container can maintain the appropriate temperature of the cells. Additional information is requested in the letter comments to provide more support for -b(4)- and sipuleucel-T stability during shipping.

Additional validation issues were found for the --b(4)------- assay used for determining cell viability, -b(4)--- assay used to measure endotoxin content, and the gram stain for microbial detection. The current criteria for calculating the results of the --b(4)---------- assays are insufficient to ensure a reliable estimate. Further, for the -b(4)------- assays there is a lack of precision in the validation method to be confident that different operators can obtain a similar result. The gram stain was not adequately validated because both gram positive and negative organisms were not evaluated.

The major challenge in manufacturing this product is not in the manufacturing protocol, as this is a relatively simple manufacturing procedure. Logistics is perhaps the more challenging aspect of producing this product due to the short shelf life of both the incoming apheresis units and the final product. Given the tight manufacturing schedule, short process time limitations,

overlapping production schedules, QC testing, and complex shipping situations, it will be difficult to generate this product at high throughput without substantial attention paid to coordinating and orchestrating these events. The BLA is deficient in describing these complex logistical issues, but more information is being provided, and these concerns were communicated in the 483 inspection discussion items.

[PA2024]
In almost all respects the section of the filing dealing with PA2024 is of exceptional quality. The manufacturing process is well-designed, robust, and validated properly, with minor, easily-correctable exceptions. The protein product is characterized using an extensive battery of state-of-the-art techniques that allow reliable assurance regarding the utility of the in-process, lot release, and stability-indicating assays selected.

The primary area of concern regarding the PA2024 reagent at the time of the pre-BLA meeting was demonstration of substantial biochemical equivalence between the material used in the pivotal trial and that produced using the commercial-scale process. The scale, type of -b(4)---- used, and -b(4)-------- scheme were all modified. Certain of the test methods, in particular the -b(4)---------, were under development at that time, and convincing data supporting equivalence by this technique were not available. The data provided in the license application resolve this concern definitively in my view. The detectable differences in the two products reside primarily in the -b(4)---------- states of -b(4)--------- (the manufacturing scale product is also of greater purity). Such variation is expected during scale up, and is highly unlikely to have any impact on the performance of the product. Moreover, extensive biological activity data confirms that products produced by the two processes perform equivalently.

Certain concerns regarding validation studies for hold times of process intermediates, upper and lower limits for certain process parameters, and a few other minor matters encountered during the review have been addressed in Amendment 10.

Letter Comments:

1. Outstanding issues from your pre-license inspection, dated February 12-16, 2007, have yet to be resolved.

2. The stability of the --b(4)---------- and the potential effect on sipuleucel-T cannot be fully evaluated from the data provided. It is not clear that the data presented in Figure 8 in section 3.2.P.2.3 are representative of the range of clinical experience. Please provide a more detailed explanation of how the stability studies of the -b(4)- were conducted.

3. Additional data are needed to validate shipping of sipuleucel-T during elevated external temperature conditions. Please provide data verifying that sipuleucel-T product attains the specified 2-8°C temperature range within a defined time period and maintains this temperature throughout the remainder of the shipment when exposed to high external temperature shipping conditions. Temperature probes should be used on the outside of the shipping container, and in the product bag containing sipuleucel-T product

manufactured from healthy donors. Please provide data showing that product quality is maintained within the limits of the acceptable ranges of temperature and time. These data should be generated from studies conducted at the New Jersey facility.

4. To support the shipping validation studies addressed in item 3, please address the following:

   a. Please establish a maximum process step time for formulation of the sipuleucel-T product in lactated Ringer's solution before packaging in the shipping container with the gel packs.

   b. Please submit data demonstrating that you can ship sipuleucel-T from the New Jersey facility and infuse it into the patient within the 18 hour shelf life. We recommend that you submit data from all clinical lots manufactured at the New Jersey facility. The data should include the destination and the time from formulation to infusion.

5. Your comparability analysis included data from product manufactured at the Seattle and New Jersey facilities. Please provide additional data from the other manufacturing sites that produced clinical product for the Phase 3 clinical trials. Please provide information on the number of lots manufactured at each manufacturing site.

6. Additional information is needed to assess the validation of the -b(4)------- method as an alternative sterility test method. Please address the following:

   a. For each of the datasets provided, please clarify where and when the studies were performed and the -b(4)------ model that was used. We note that the --b(4)---------- Model is used in Seattle and the -b(4)---------- Model is used in New Jersey. Please discuss the differences in the two systems, including any differences in the detection algorithms. If this information is contained in another regulatory file you may submit a letter of cross-reference obtained from the manufacturer authorizing the Agency to refer to information contained in such file.

   b. We note that you plan to "further demonstrate the suitability of the -b(4)------- using ---b(4)----------." Please submit data from these additional studies.

   c. If you intend to use the -b(4)-------- method to test sterility of -b(4)-------, please submit data to demonstrate that the -b(4)----- formulation does not have any bacteriostatic and fungistatic effects in this method.

7. Additional data or justifications are needed to support your analytical method validations. Please address the following:

   a. We note that both the --b(4)---------- methods are tested in --b(4)----------. For each of these assays, please establish

a maximum variability between results of -b(4)---------- samples. Please describe what procedures will be followed if the maximum variability is exceeded.

b. We note that only gram positive organisms are used for the validation of the gram stain assay. Please include gram negative organisms as part of the validation.

c. Please revalidate your -b(4)---------- for accuracy and intermediate precision. Please include precision studies that demonstrate the ability of operators to differentiate between viable and non-viable cells.

Table of Contents for CMC Review

Tables and Figures

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Nomenclature for Sipuleucel-T

Recommended International Nonproprietary Name (INN)	None
Compendial Name	None
Chemical Name	None
Company Codes	APC8015, Provenge®
United States Adopted Name (USAN)	sipuleucel-T
Chemical Abstracts Service (CAS) Registry Number	Not Registerable CA Index Name: Prostate-specific antigen PA2024-containing antigen-presenting cell

3.2.S.1.2 Structure

Sipuleucel-T has no defined chemical structure, because it is an autologous cellular product.

3.2.S.1.3 General Properties

Sipuleucel-T, also referred to as APC8015, is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen presenting cells (APCs), that have been activated in vitro with a recombinant fusion protein.

The recombinant fusion protein, PA2024, is composed of prostatic acid phosphatase (PAP), an antigen expressed in prostate adenocarcinoma, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. PA2024 is an active ingredient unique to sipuleucel-T. Refer to 3.2.A.4, Novel Reagent for a full description of PA2024 chemistry, manufacturing, and controls.

Sipuleucel-T is an autologous product, for which the terms “batch” and “lot” are equivalent. In all cases, the cells from a single apheresis component, which are obtained from the patient to be treated, yield a single lot of sipuleucel-T. The resultant lot of final product is packaged in a single infusion bag and administered in a single dose.

For sipuleucel-T, the biological substance and biological final product are one and the same.

Composition of Sipuleucel-T

Component	Quantity per Unit
Autologous mononuclear cells, including To contain	≥ 50 x 10^6 $CD54^+$ cells
APCs loaded with recombinant prostate antigen Lactated Ringer's Injection, USP	qs to 250 mL
Infusion bag, sterile, 300 mL	One

3.2.S.2 Drug Substance Manufacture

3.2.S.2.1 Manufacturers

The manufacture of the cellular component of Sipuleucel-T occurs at:

Dendreon Corporation
220 East Hanover Ave.
Morris Plains, NJ 07950

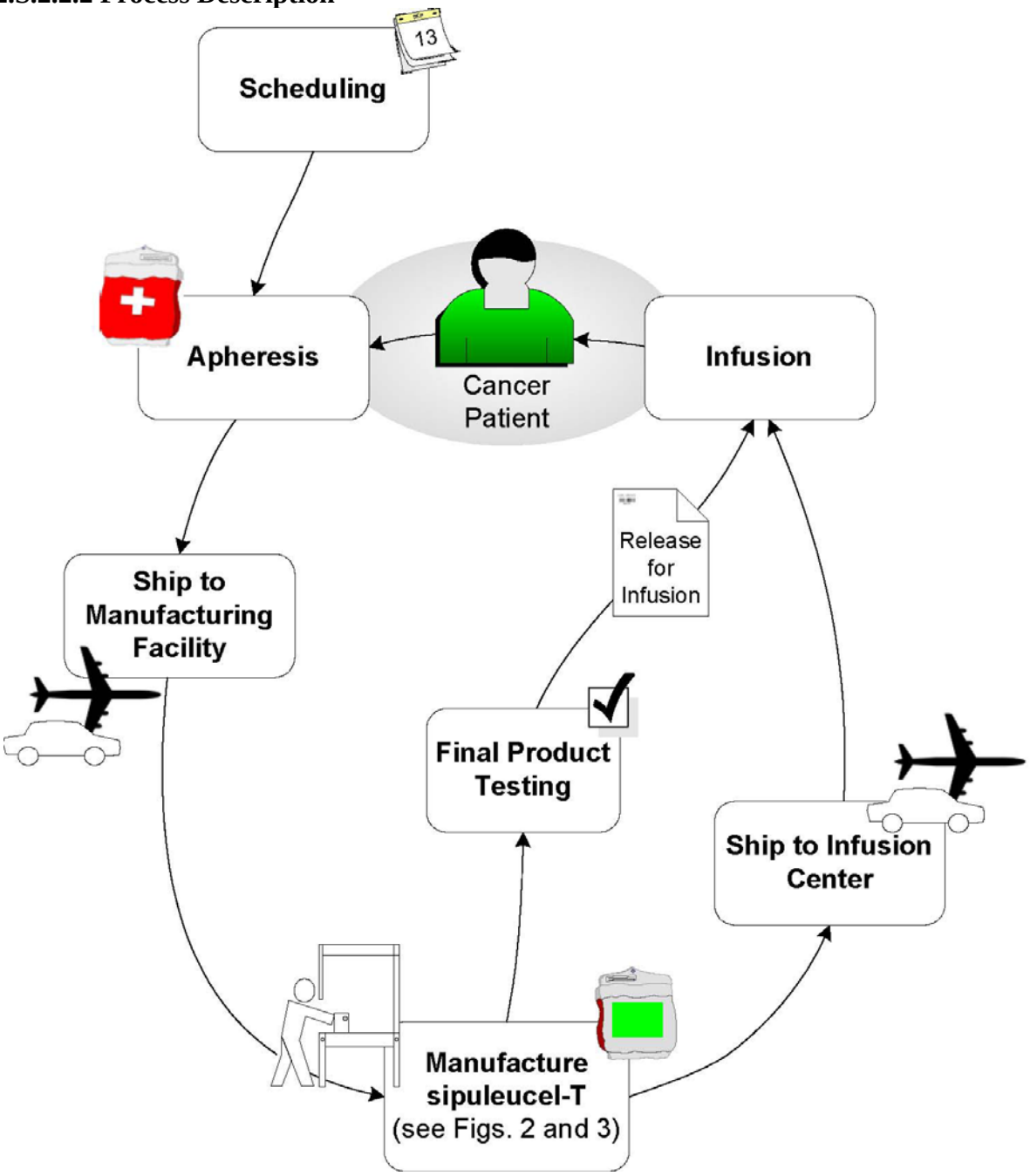
3.2.S.2.2 Description of Manufacturing Process and Process Controls

3.2.S.2.2.1 Batch Size and Scale Definition

Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen presenting cells (APCs), that have been activated in vitro with a recombinant fusion protein. The recombinant fusion protein, PA2024, is composed of prostatic acid phosphatase (PAP), an antigen expressed in prostate adenocarcinoma, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF).

Each lot of sipuleucel-T is produced from a whole apheresis component (APH) obtained from a single patient, and returned to that patient after in vitro activation.

3.2.S.2.2.2 Process Description



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Dendreon defines critical operating parameters as those that potentially compromise the quality of the product if the acceptable ranges are exceeded. These are described in greater detail under process validation.

3.2.S.2.5 Process Validation and/or Evaluation

Process Validation

The sipuleucel-T process validation was completed at Dendreon's manufacturing facility in Morris Plains, NJ, with the production of --b(4)------- lots of sipuleucel-T manufactured from healthy donors.

Dendreon's NJ facility is designed to accommodate the concurrent manufacture of -b(4)----- lots of products. --b(4)---------- workstations are --b(4)----------. By requiring b(4) production lots for process validation, it required that -b(4)----- workstations were in use -b(4)----, and -b(4)---lots were at -b(4)---------- stages in the manufacturing process for at least part of the validation study. Because the -b(4)- manufacturing process was initiated for -b(4)- on -b(4)- day, and for the remaining -b(4)- on the following day.

Reviewer comment: On inspection the b(4) lot validation became a pivotal issue because this does not represent the full capacity of the facility. DMPQ felt that true process validation should be performed at maximum production capacity. Refer to 483 and inspection report.

Because the b(4) sets of runs were processed on -b(4)--- days, all b(4) lots were present in the incubator room at the same time.

The process validation protocol was executed in Module b(4) of the NJ manufacturing facility using the commercial processing steps and all associated procedures. This included contamination control and product segregation procedures such as pre-and post-process cleaning, line clearance and changeover procedures, and secondary containment of product and QC samples.

Note: -b(4)---------- was used. Is this a concern in terms of robustness? Probably not. However, DMPQ had a concern about the lack of validation of module b(4) on inspection.

The APH were transported from multiple apheresis centers using packaging, transportation, and receiving procedure.

Note: Its good that multiple apheresis centers were used.

The computer system that will be used for tracking was not operational during the process validation, which required that some of the documentation that will be automated had to be entered manually.

Reviewer comment: Not having the computer system in place during validation is a small concern, but probably not significant. It may improve things such as time required for each step since there was a lot more manual record keeping that would presumably be accelerated with automation (reagent lot numbers, creating labels, etc)

Exceptions/deviations during the process validation were documented using the exception report. This report captured: 1) a description, 2) a root cause analysis, 3) a classification—critical or non-critical, 4) corrective action taken, and 5) closure.

Parameters and acceptance criteria for process validation

*Lot release criteria

[b(4)]

Aseptic Processing Validation

Aseptic process validation was executed according to protocol QVD 50895, Aseptic Process Validation (APV) for Sipuleucel-T for New Jersey IMF. Aseptic processing of sipuleucel-T was validated using a --b(4)----------. The APV was performed in Module b(4) in the New Jersey immunotherapy manufacturing facility (IMF). -b(4)-

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[**b(4)**]

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--b(4)----------

3.2.S.3.2 Impurities

Product related impurities:

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- ---b(4)----------

Process related impurities:

Reviewer comment: I am satisfied with the development studies and do not feel that these residuals/impurities need to be tested for in the final product.

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  - ---b(4)---------- ----------
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3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specifications

The table below lists the lot release specifications for sipuleucel-T. The description of methods, methods validation, and justification for specifications will follow. The development studies to support the choice of tests and parameters is described in the drug product section (3.2.P.2.3 Manufacturing process development).

Lot Release Specifications

Attribute	Test Parameter	Sample	Acceptance Criteria
In-process Testing			
	--b(4)-------	-b(4)--	-b(4)--
	---b(4)---- ----------	-b(4)--	-b(4)--
	--b(4)---- -----	-b(4)--	-b(4)--
	-----b(4)---------- -------	-b(4)--	-b(4)--
Final Product Testing			
Identity	Identity	Final Product	-b(4)--
Potency	CD54 upregulation	Final Product/Post --b(4)--	-b(4)--
	Number of $CD54^+$ cells	Final Product	-b(4)--
Purity	Viability	Final Product	-b(4)--
Safety	Endotoxin content	Final Product	-b(4)--
	Microbial contamination	Final Product	-b(4)--
	Sterility (Dayb(4) read)	Final Product	-b(4)--

Phase 3 Lot Release Specifications History

[b(4)]

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--b(4)--- ----------

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Sterility

Background: Dendreon previously used under IND the 21CFR 610.12 method to determine sterility. These tests were performed by a 3rd party. In November 2000 Dendreon installed in their Seattle facility a ----------b(4)----------. Dendreon performed a limited qualification study using that instrument. The use ----------b(4)---------- systems is now commonplace, and several studies have been documented in the literature comparing the CFR method with --b(4)---------- systems [b(4)]. For the New Jersey facility Dendreon installed a -----b(4)---------- system, which is based on the same detection principles. The --b(4)----------) is an FDA-approved diagnostic device (--b(4)----------). The --b(4)-- system eliminates the -b(4)------- interpretation by laboratory

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[b(4)]

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---*b(4)*-- ----------

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A copy of QVD 50893 was provided in Section 3.2.S.7.1. However, it is lacking in details as to how the study is intended to be conducted beyond acceptance criteria and that b(4) lots will be shipped.

Sipuleucel-T final product lots (manufactured from healthy donor cells) will be shipped according to commercial procedures. All lots will be analyzed against the final product specification before and after shipment to verify that product quality is maintained during transport. Results from this study will be available for review at inspection.

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---***b(4)***--- ----------

Review issues:

- None of the shipments (using simulated product) were sent from the NJ facility. The NJ facility was the receiving end.

- Shipping studies were not designed based on shipping experience for lots manufactured under IND, and though they are stated to be designed based on expected shipping routes and conditions, this is unclear. No documentation was provided that estimates these conditions.
- Temperature spikes in the -b(4)-- test design are meant to reflect temperature extremes that would be encountered at loading docks and on the airport tarmac. It is unclear how well these reflect actual shipping conditions likely to be encountered in major distribution routes. One of the summer -b(4)-- tests using simulated final product barely met the 2-8 degree range for final product summer --b(4)------ and the study was not repeated.
- Lack of documentation covering logistical shipping issues. Of concern is when the facility is operating at high capacity will the logistics become a serious barrier to successful product manufacturing.
- A discussion was held with Mike Poor of Dendreon during inspection of the NJ facility about shipping validation and scheduling of shipments. The question was raised if 18 hours is long enough to cover shipping at all locations around the US. He said yes, that they have a lot of experience shipping product under IND and they have a shipping template in place. The Seattle Scheduling group has an algorithm they use and a set of procedures they follow. I asked if this was written down anywhere, even as internal documents and he said no. Mr. Poor stated that it was "to complicated to describe or put in an SOP".
- It is unclear if the shipment of only --b(4)-------- lots of final product from Dendreon Seattle to Dendreon NJ represents a rigorous enough test to reflect temperature extremes and shipping conditions that would be encountered for commercial manufacturing.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

Shelf life extension with -b(4)----------. (*Note: this information is presented in section 3.2.P.3 subsection 2.2.1, but is reviewed here for the purpose of clarity).* Prior to 2006 the shelf life was set at -b(4)---------- and for final product). Since a -b(4)--- shelf life would not only limit the locations a commercial product could be distributed, it would also affect the logistics of manufacturing and potentially reduce the capacity to manufacture the product. For phase III D9901 andD9902A studies the average interval between leukapheresis and the start of manufacturing was -b(4)------. The clinical sites and manufacturing sites were coordinated to work within a -b(4)---- shelf life for the final product, though no shelf life was established for the APH.

In 2006 Dendreon submitted an IND amendment demonstrating the addition of --b(4)------ ----------. Dendreon has defined -b(4)- stability in terms of ---b(4)---------- ---------- Two stability studies were performed that evaluated -b(4)------- as a function of -b(4)- age, and the affect that ---------- ---b(4)---------- in the product bag has upon stability.

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3.2.S.7.3 Stability data

Background: Dendreon performed stability studies on the -b(4)---------- the final product. The final product stability data is presented in sections 3.2.S.7.1 and 3.2.S.7.3. The data is presented in greater detail in section 3.2.S.7.3. They also include a protocol for a proposed post-approval stability study. Data on -b(4)----- stability is presented in section 3.2.S.7.3. The criteria for the stability tests and the post-approval plan are very similar, with the later including test parameters generated from the outcome of the stability tests. The stability data was also used in support of their shipping validation studies. Although the -b(4)--------- was included in these studies, it is not included as a lot release specification. This is probably due to the highly variable nature of this particular assay.

[b(4)]

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[b(4)]

Final product. All lots of sipuleucel-T met the stability acceptance criteria throughout the b(4) hour study when stored at the recommended storage temperature of 2 to 8°C. The 18-hour shelf life is supported by b(4) key parameters (------b(4)----------), each of which appear to be stability-indicating to some degree. For these assays, the stability results showed a detectable decline over time when sipuleucel-T was stored at the stress temperature of -b(4)--

In 2 of the 3 assays evaluating indicators of product potency and/or functionality, the results showed a decline over time at the recommended storage temperature of 2 to 8°C. For one of these assays, --b(4)----------, quantitative acceptance criteria cannot be set due to inherent variability in the assay. The other assay, which evaluated ---b(4)---------- ----------, reported as -b(4)- normalized to the -b(4)- of the initial time point, provides quantitative stability-indicating results. As such, these data were subjected to statistical analysis. (Refer to Section 4.2.2 of this summary and to 3.2.S.7.3, Stability Data, Section 6.0.)
A summary of stability results is presented in Table 4. Results include both Phase 1 and Phase 2. The ranges in the table represent the minimum and maximum values observed in any lot at any time point in the --b(4)------ studies.

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Stability data provided on the shipped final product.

Shipping validation information is contained in two locations: 1) container closure system where the shipping container is described and the container is tested to see if it maintains the specified temperature range using simulated product, and 2) in section 5.0 of 3.3.S.7.1 where stability of the product was examined over time at a constant shipping temperature b(4) or under conditions of stress (--b(4)----). No studies were presented in the BLA demonstrating that when the final product is shipped it is stable. The BLA contained a notation that such data would be present at the time of inspection. Data was provided on b(4) lots manufactured and shipped in October, 2006 from the --b(4)----------. Since this was purely a stability study and no temperature data was monitored, that information has been added here. The shipping validation studies were detailed in document # 51034 dated Jan 11, 2007 and QVD 50893 dated Oct 6, 2006.

-b(4)- lots were manufactured for these studies for round trip shipment so that the product could be received and re-evaluated for product stability and integrity. These b(4) lots were manufactured at the --b(4)---------- NJ facility. The shipments did not originate from the NJ facility, instead they were sent from the ---b(4)----------, and all lots were shipped at the same time using --b(4)----------. No data, however, was included on the shipment of -b(4)- material to the -b(4)-------. The b(4) lots were all manufactured beginning on 10/10/06 through 10/12/06 and shipped on 10/12/06.

In-process specifications for the b(4) lots were as follows:

[b(4)]

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and the remainder of the -b(4)-------- test period the product was held in the shipper. It is not clear how well this represents a typical shipment.

---b(4)--- ----------

Summary of all stability studies: The shelf life for -b(4)--------- and the final product is 18 hours. Largely for shipping logistical reasons Dendreon has set the specification to be the same -b(4)----, even though the stability studies suggest that the final product might be more stable than the b(4). Stability is important for any cellular product, but it is especially important for sipuleucel-T because of the complex logistics involved in coordinating shipping and manufacturing this autologous therapy. It would be to Dendreon's advantage to validate shipping for as long as possible, because it would provide for a larger logistical margin of error. In 2006 the shelf life of the --b(4)---------- the final product) was extended to 18 hours from b(4).This was in response to problems with a small number of lots being infused into patients past the expiration time, sometimes with a final product age of as much as -b(4)--------. During inspection it was stated that ----------b(4)-- ----------

b(4) stability is greatly -b(4)------ with the --b(4)---------- ----------. Though the studies were only carried out for -b(4)-, the regression curves suggest that the b(4) may validate for even longer. These were not as detailed of studies as were stability studies conducted for validating stability on the final product, but were still meaningful. Stability studies for the final product demonstrated that the product is stable for 18 hours, --b(4)-----. Though these studies were carried out for -b(4)---, shipping studies were carried out for only --b(4)----------

For the final product it is difficult to fully interpret the validity of the potency measurements ($CD54^+$ cell number and CD54 upregulation) because Dendreon did not actual determine what is needed to ensure a potent product. However, a number of publications suggest that a -b(4)-- upregulation in CD54 would be indicative of activated monocytes. Assuming that the specifications set for lot release criteria are valid, then the data show that the product is stable for 18 hours and the shelf life is reasonable. ----b(4)----------

Another confounding factor in the evaluation of the stability data is the lack of detail on the logistics involved in the shipping the b(4) manufacturing the product, performing QC testing, and shipping and infusing the commercial product. This issue is elaborated on in more detail in the container closure section review. Data from studies conducted at -----b(4)----- is very useful, but without knowing what shipping conditions the products would actually be exposed to and how long it takes a commercial lot to reach the ramp down temperature during actual shipment to distant locations and/or locations with less moderate climates, one cannot be completely confident of the shelf life.

The greatest weakness to the conducted stability and shipping studies is the very limited data on shipping actual product and not simulated product, as was done in the container closure

studies. The study conducted withb(4) lots of the final product sent roundtrip to -b(4)--- were successful, but of questionable adequacy.

All parameters examined, with the exception of CD54 upregulation, show the product is very stable and the shipping container performed well under the specific conditions tested. The -b(4)---------- in CD54 upregulation -b(4)----------shipment estimations would not be significant for these lots, as they are still way above lot release specification of b(4). They are also representative of an average production lot since the average level of CD54 upregulation among b(4) lots was --b(4)----------

Review issues:

1. Limitations in the conducted product stability studies:

- Though it is clear that -b(4)-------- substantially -b(4)---------- stability, product variability is great at --b(4)-------.
- Stability studies could have been designed to better reflect the temperature shifts and conditions the product is likely to be exposed. For example, an additional stability study conducted at --b(4)---------- might be very valuable.
- Lot release criteria for $CD54^+$ cell number and CD54 upregulation are based only on manufacturing experience and do not fully take into account clinical outcomes. Therefore, it somewhat difficult to evaluate the validity of the stability specification ranges.
- Only b(4) shipments were tested where cells were included and tested for stability
- No products were manufactured nor shipped from the NJ facility
- All b(4) lots were shipped simultaneously
- The shipping conditions did not test the "summer" and "winter profiles" established for the container closure. They were shipped under moderate climate conditions.
- No temperature probes were included with the b(4) shipped lots
- More data is needed on how much CD54 upregulation is -b(4)- in the final product as a consequence of shipping and holding the product in the shipping container.

A letter comment was included asking for additional shipping data from lots produced and shipped from the NJ facility. Temperature probes should be included in order to monitor internal and external shipping container temperatures, and a shipping destination(s) should be chosen that would represent shipment under "elevated" shipping conditions.

2. Dendreon proposes as part of their post-marketing agreements to conduct additional stability studies. It would be preferable if this included more studies on ---b(4)---------- ---------- It would also be helpful if they provided more information on the impact of the wide range in --b(4)------ they see, even with the inclusion ---b(4)----------

A letter comment was included asking for additional information demonstrating that acceptable lots of sipuleucel-T can be generated from apheresis products throughout the full range of $CD54^+$ cell recovery results.

3. An important post-marketing commitment would be a requirement to provide detailed shipping information for all commercial lots generated during the first year of licensure. This would include temperature probes included with all incoming and outgoing lots, b(4) age, and expired shelf life at the time of infusion. This would strengthen not only the stability studies, but help document the logistics involved. Another approach would be to collect the same data from the ongoing clinical trial.

A letter comment was included asking for more information on previous shipments of clinical products to various clinical sites, including shipping information on all clinical lots produced in the NJ facility. Once we have this information we can evaluate whether Dendreon has accumulated enough manufacturing and shipping data to address our concerns, or if additional studies will be required.

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

The proposed post-approval stability program is designed to provide ongoing assurance that the product continue to meet specification acceptance criteria at the end of its approved shelf life when stored and handled properly. The post-approval program proposes to conduct stability studies at the recommended storage temperature (2 to 8°C) on a -b(4)---- basis at each Dendreon manufacturing facility, with each study performed -b(4)----- sipuleucel-T manufactured from apheresis component obtained from a healthy donor positive for HLA-DR1. This would represent at least b(4) lots per year from each manufacturing facility. (Additional lots would be tested as needed in the event of a process change.)

The results from these studies will be submitted to the FDA in annual reports. Dendreon commits to report any significant change or deterioration in the drug product according to current applicable regulations. After b(4) years, Dendreon will assess the program and potentially ---b(4)----------

[b(4)]

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

(This section of the review also covers the first couple of sections from 3.2.P.2 which deal with excipients, drug substance, and formulation development)

For sipuleucel-T, the biological substance and the biological final product are one and the same. As an autologous cellular product, sipuleucel-T has no defined chemical properties. Instead, it has been characterized on a ----b(4)---- ----------
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----------The key cellular characteristics for sipuleucel-T are viability and potency.

Sipuleucel-T consists of antigen-loaded, washed cells. The product is formulated as a cell suspension in Lactated Ringer's Injection, USP, to be administered by intravenous infusion.

Lactated Ringer's Injection, USP, is used as a physiological cell suspension medium. It was chosen because it is a ------b(4)----------, commonly used in clinical practice. Lactated Ringer's Injection, USP, has been shown to be compatible with blood components.

Note: Reference for this statement shows that lactated ringer's does not affect cytotoxicity of -b(4) cells. I don't believe a formal biocompatibility study was done nor was a specific study done with sipuleucel-T.

3.2.P.2 Pharmaceutical Development

3.2.P.2.2.3 Physicochemical and biological properties

Introduction
---b(4) ----------

[b(4)]

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Approach for statistical analysis

3.2.P.2.3

Comparability of clinical and commercial product

Background: In support of commercial production of sipuleucel-T, Dendreon is seeking licensure of a manufacturing facility located in Morris Plains, NJ. The following observations establish the comparability of sipuleucel-T manufactured for clinical use to sipuleucel-T manufactured in the NJ facility:

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Review issues: The current study is adequate at demonstrating comparability between the existing Seattle facility and the newly operational NJ facility. Given the substantial inherent variation in the product, however, any future comparability studies (if conducted), should be done with split lots if at all possible.

Since the NJ facility has been used to generate additional clinical lots for the ongoing clinical trials additional lots have been made in the NJ facility since the submission of the BLA. It would have been beneficial to see the in-process and final product outcomes for these additional lots.

A4-3.2.S Novel Reagent Drug Substance Part 1 of 2
Total Pages 2395

3.2.S DRUG SUBSTANCE [PA2024]

A4-3.2.S.1 GENERAL INFORMATION

A4-3.2.S.1.1 NOMENCLATURE

1.0 NOMENCLATURE

Prostate Antigen (PA2024). For this material, the drug substance and drug product are one and the same. It is used in the manufacture of Sipuleucel-T. Because fragments of PA2024 are bound to the final product, I consider it an active ingredient.

A4-3.2.S.1.2 STRUCTURE [PA2024, DENDREON]

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The Pre-Approval Inspection for PA2024 was not conducted.

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.R Regional Information
3.2.R.1 Executed Batch Records
Executed batch records are provided and appear satisfactory.
3.2.R.2 Comparability Protocols
See **3.2.P.2.3.4.**
3.2.R.3 Methods Validation Package
See review of 3.2.S.4.1 and 3.2.S.5.1.
5.3.1.4 Immunogenicity Assays (-b(4)-)
Not applicable

List of amendments received during BLA review period

	Topic	CMC related	Reviewed in BLA section	Included in 483 EIR
Amendment 001	Telecon minutes between Dendreon and DCGT & DMPQ about facility validation	Yes	No	Yes
Amendment 002	3.2.A appendix amendment covering System and Equipment Risk Assessment Forms	No	No	No
Amendment 003	Telecon minutes between Dendreon and CBER discussing submitting additional immune response and efficacy analyses; provided additional immune response data and updated clinical pharmacology	No	No	No
Amendment 004	Telecon minutes between Dendreon and DCGT regarding a possible increased risk of cerebrovascular accident (CVA) events	No	No	No
Amendment 005	Additional information provided for sterility test method equivalence--b(4)--- ----------retention samples	Yes	3.2.S	Yes
Amendment 006	Sample of draft carton label on shipping container	No	No	No
Amendment 007	Submission of additional immune response and 4 month safety update	No	No	No
Amendment 008	Additional data provided on results from Module b(4) validation	Yes	No	Yes
Amendment 009	Additional clinical survival and immune response data, and supportive documentation on product manufacturing logistics, multiproduct policy, and 483 response	Yes	No	Yes
Amendment 010	Provided addiitonal information on PA2024 issues discussed in a 3/15/07 telecon between Dendreon and DCGT	Yes	3.2.P and 3.2.A	No

CMC Appendix Section

Appendix A: List of abbreviations
Appendix B: Summary of clinical lot properties
Appendix C: Quartile analysis of product lots: CD54 upregulation.
Appendix D: Lot characteristics and correlations
Appendix E: Salvage product
Appendix F: Product deviations
Appendix G: Potential correlations of product qualities with infusion-related adverse events among D9901
Appendix H: Immune monitoring
Appendix I. Lot release specifications

Appendix A: List of definitions and abbreviations

% CV: Percent coefficient of variation, the standard deviation of the values
% HCT: Percent hematocrit, the volume/volume percentage of RBCs
% Hematocrit (HCT): measures RBC concentration as volume % of whole blood
% Granulocytes: Auto (GRAN) = % Neutrophils (NE) + % Eosinophils (EO) + %Basophils (BA)
---b(4)----------
% v: Viability
"+": Out of Linearity (---b(4)----------)
"++++": Out of Reportability (and linearity) (---b(4)-- ----------
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--b(4)----------
Action Level: Concentration of viable and non-viable particulates in a controlled environment that, when exceeded, signals a drift from normal operating conditions and requires an investigation and corrective action
ACS: American Chemical Society
Alert Level: Concentration of viable and non-viable particulates in a controlled environment that, when exceeded, signals a potential drift from normal operating conditions.
--b(4)-- ----------

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APC: Antigen presenting cell

APC8015: sipuleucel-T, or Provenge®

Apheresis (APH): The terms "Leukapheresis" and "Apheresis" are used interchangeably in the batch record and cell processing SOPs.

---b(4)--- ----------

Assay: A triplicate analysis of the same sample (--b(4)--- **----------**

--b(4)-- ----------

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APV: Aseptic process validation

B/F: Bacteriostasis and Fungistasis

Baseline Correction: Corrects baseline under the specified measurement parameters.

Background Control: --b(4)**----------**

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Biological substance/product: For sipuleucel-T, the biological substance and biological final product are one and the same. The biological substance section (3.2.S Drug Substance) contains the bulk of the chemistry, manufacturing and controls information for sipuleucel-T. Many of the biological product sections in 3.2.P, Drug Product, simply refer to the corresponding section in 3.2.S. Only those topics that are not addressed under 3.2.S contain additional information. The primary examples of such sections are 3.2.P.2, Pharmaceutical Development and 3.2.P.4, Control of Excipients.

BR: Batch Record: The manufacturing batch record and all associated attachments, forms, print outs, electronic records, etc. that are generated or referenced for a specific lot of product. The manufacturing batch record and all associated attachments, forms, print outs, electronic records, etc. that are generated or referenced for a specific lot of product.

BSC: Biological safety cabinet

--b(4)--- ----------

CBC: Complete blood count

--b(4)--- ----------

CD-54: Intercellular adhesion molecule-1, a glycoprotein found in the immunological synapse.

Cellular composition: Percentage of each common cell type within a cell sample.

--b(4)--- ----------

CFR: Code of Federal Regulations
CFU: Colony forming units
---b(4)--- ----------

--b(4)--- ----------
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Complete Blood Count (CBC): A test measuring blood (or a blood derivative) for concentration or percent composition of various components (e.g., Red Blood Cells, White Blood Cells, Platelets, etc). For this test method, report the following parameters as defined by each product QCSW
--b(4)-- ----------

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CPRF: Cell Product Request Form.
--b(4)--- ----------
CV: Coefficient of variation (standard deviation ÷ mean, expressed as a percentage)
Cytokine: Cellular mediator involved in regulating the immune response.
DI: Deionized water
Dilution: Dilutions are expressed as the ratio of the quantity of a desired solute (sample) contained in a solvent (diluent). For example, a 1:2 dilution is made by adding one part sample to one part -b(4)-- to make a total of two parts.
DNDN: Dendreon Corporation, 3005 1st Avenue, Seattle, Washington
--b(4)-- ----------
DR: Deviation Report
Donor No.: A unique identifier assigned to the apheresis donor by --b(4)----------
--b(4)--- ----------
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--b(4)----------
EU: Endotoxin unit
---b(4)----------
Fc: Heavy chain fragment of an antibody molecule, containing the domains that interact with effector molecules and cells
GM-CSF: human Granulocyte Macrophage Colony Stimulating Factor
Gram (+): microorganisms that retain the primary stain and appear dark purple in color.
Gram (-): microorganisms that lose stain (decolorize) and take up the counter stain, appearing pink in color.

GRAN: Granulocytes, which includes neutrophils (NE), eosinophils (EO), and basophils (BA), reported as a percentage of WBCs

----b(4)--- ----------

HCT: Hematocrit

hGM-CSF: Human granulocyte-macrophage colony stimulating factor.

--b(4)--- ----------

HLA-DRβ1: Human Leukocyte antigen- DRβ1

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IMF: Immunotherapy manufacturing facility (i.e., the NJ facility)

Ig: Immunoglobulin

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---b(4)--- ----------

Final Product: Final product formulation of sipuleucel-T, APC Placebo or APC 8015F

---b(4)-- ----------

Formulation Buffer: -b(4)---- ----------

FP: Final Product Specification Acceptance Criteria

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LIMS: Laboratory information management system, which includes data analysis templates to be used in QC testing of the proposed sipuleucel-T commercial product

--b(4)--- ----------

LOQ: Limit of Quantitation (blood counts)

Lot: Sipuleucel-T, also referred to as APC8015, is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen presenting cells (APCs), that have been activated in vitro with a recombinant fusion protein. The recombinant fusion protein, PA2024, is composed of prostatic acid phosphatase (PAP), an antigen expressed in prostate adenocarcinoma, linked to granulocyte-macrophage colony stimulating factor (GM-CSF), an immune cell activator. Each lot of sipuleucel-T is produced from a whole apheresis component (APH) obtained from a single patient, and returned to that patient after in vitro activation. In this submission, the term "leukapheresis", for the collection of white blood cells by apheresis, is used interchangeably with "apheresis". Similarly, the apheresis component is also termed "leukapheresis component". By definition, each sipuleucel-T product is a different lot and therefore comparisons between lots cannot be made.

--b(4)--- ----------

LPR: Leukapheresis Procedure Report.

LR: Lactated Ringer's, Injection, USP

--b(4)--- ----------

M: Mean background control OD

---b(4)-- ----------

--b(4)--- ----------

--b(4)--- ----------

--b(4)--- ----------

--b(4)--- ----------

---b(4)-- ----------

--b(4)-- ----------

Neat: Not diluted

--b(4)--- ----------

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--b(4)--- **----------**

PAP: Human prostatic acid phosphatase

PA2024: A recombinant fusion protein comprised of human Prostatic Acid Phosphatase (hPAP) and human granulocyte macrophage colony stimulating factor (hGM-CSF) that is --b(4)----------

--b(4)-- **----------**

-b(4)-- **----------**

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PDA: Parenteral Drug Association

--b(4)-- **----------**.

pH value: The unit of measurement of the acidity or alkalinity of a solution, expressed as the negative logarithm of the hydrogen ion concentration (i.e. pH =-log $[H^+]$).

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Product: Active immunotherapy product (i.e. sipuleucel-T, APC8015F, APC Placebo)

PV: Process validation

PW: Purified water

--b(4)-- **----------**

q.s.: Quantity Sufficient (i.e. add volume until a pre-determined volume is reached).

QCSW: Quality Control Summary Worksheet (FRMs 60114, 60131, 60133 and 60134)

$\mathbf{r^2}$ value: (Coefficient of Determination): Quantifies the goodness of fit

Reducing Agent: Ensures complete and consistent --b(4)----------.

R: Retain Sample.

--b(4)-- ----------
RBC: Red blood cell concentration (reported as -b(4)-
--b(4)--- ----------
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--b(4)-- ----------
--b(4)-- ----------
RPM: Revolutions Per Minute.
--b(4)-- ----------
--b(4)-- ----------
--b(4)-- ----------
SC: Separation Container.
SD: standard deviation
---b(4)- ----------
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--b(4)--- ----------
--b(4)-- ----------
Static State of rest: human presence and activity (none except for monitoring personnel) and equipment operation (not operating or operating but not in use)
Step: Process step which yields a sample (---b(4)-- ---------- Final Product)
STM: Standard Test Method

T: Threshold value for the sipuleucel-T --b(4)------
--b(4)-- ----------
TC: Total Cell Count --b(4)---------
Test Article: Any component or component material to test under the given conditions.
Test Sample: An aliquot/fraction of cells derived from either the active immunotherapy manufacturing process (--b(4)----------) or final product <FP>. -b(4)-containing cells from a specific in-process or final product step. sipuleucel-T or APC Placebo final product sample
--b(4)----------
--b(4)--- ----------
Tm: Melting temperature
--b(4)---- ----------

TM: Test Method
--b(4)--- ----------
Transmittance (%T): The fraction of incident radiation transmitted by the solution.
TS: Technical Specification
--b(4)--- ----------
--b(4)--- ----------
TTD: Time to Detection (sterility)

Upper Asymptote: Maximum proliferation of cell growth
Upregulation: Increase in molecules on the cell surface, specifically ICAM-1 (CD54)
USP: United States Pharmacopoeia

--b(4)--- ----------
VA: Average of all -b(4)--------- cell counts
Visible Particulate: Observable foreign and particulate matter
VL: Validation Limit Acceptance Criteria

---b(4)-- ----------

WFI: Water for Injection
WBC: White Blood Cell. White Blood Cell (WBC) concentration

Appendix B: Summary of clinical lot properties

In this section a description of key product features is summarized for the manufactured lots generated for clinical trials D9901 and D9902A. Information is also provided on those lots included in the BLA for the ongoing studies D9902B and P-11. The summary is intended to help highlight the extreme inherent product variability, but also the illustrate the consistency between lots generated for the clinical trials.

	Phase	Status	Number of subjects[1]	Product[2]	Placebo	number of infusions[3]	Theoretical # of lots produced	Infusion times (wks)
D9801	I	completed	15			4	-b(4)-	0, 2, 4, 16
9610	I/II	completed	31			4	-b(4)-	0, 4, 8, 24
9702	I/II	completed	34			2	-b(4)-	0, 4 or 0, 2
D9903	II	completed	56			3	-b(4)-	0, 2, 4
D9905	II	completed	18			3	-b(4)-	0, 2, 4
PB01	II	completed	28			3	-b(4)-	0, 2, 4
D9901	III	completed	127	82	45	3	-b(4)-	0, 2, 4
D9902A	III	completed	98	65	33	3	-b(4)-	0, 2, 4
P-11	III	ongoing	176	116	59	3 (4)	-b(4)-	0, 2, 4 (at time of PSA progression)
D9902B	III	ongoing	179	198	96	3	-b(4)-	0, 2, 4

[1] For P-11 and D9902B, as reported in 2-6-06 snapshot

[2] For P-11 and D9902B, as reported in presentation to 3-30-07 advisory committee

[3] For P-11 the number of fusions can be 3 with a 4th booster infusion at time of PSA progression

For all phase III trials there was the intention to generate a production lot of final product for each patient. A leukapheresis was to be performed 2 weeks apart and the autologous product infused into the patients 3-4 days later. For trail P-11 there was an optional 4th booster that was generated and administered at a later date. Not all patients received 3 infusions. In some cases a 3rd lot was not made, and in other cases a lot was made, but not infused. The quartile analysis described in Appendix C was performed only for those patients that where 3 lots had been made.

Number of autologous lots generated for infusion for phase III studies

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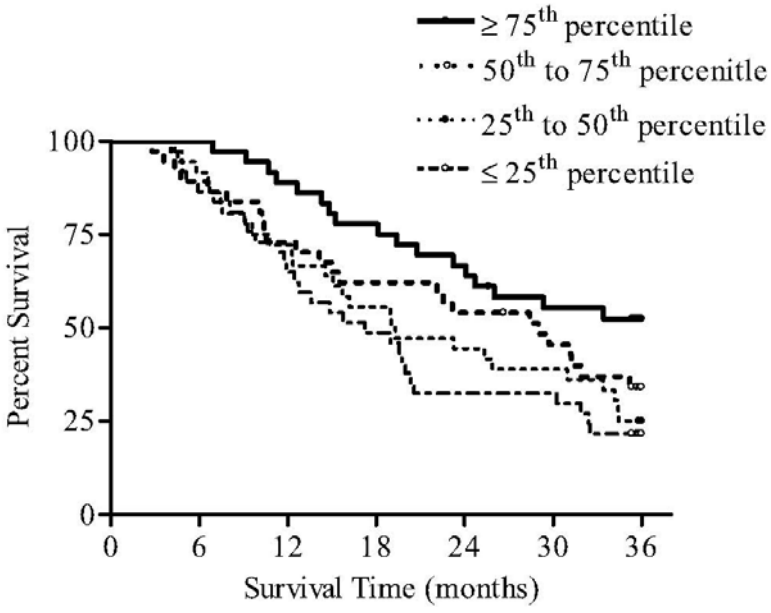
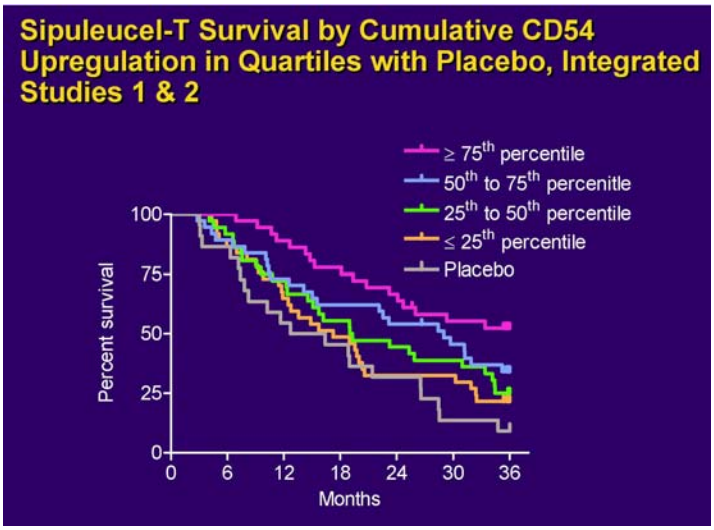
Appendix C: Quartile analysis of product lots: CD54 upregulation.

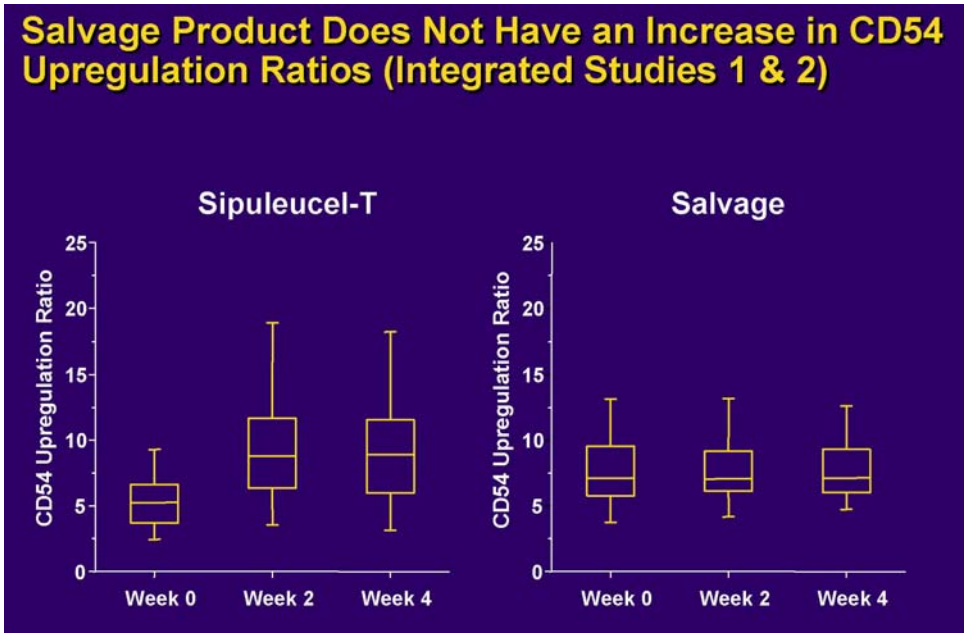
Dendreon had included in the BLA tertile and quartile analysis, and later presented to the OCTGT Advisory Committee an updated quartile analysis showing a correlation of CD54 upregulation with survival.

Figure 34 Sipuleucel-T Survival by Cumulative CD54 Upregulation in Quartiles, Integrated Studies 1 and 2



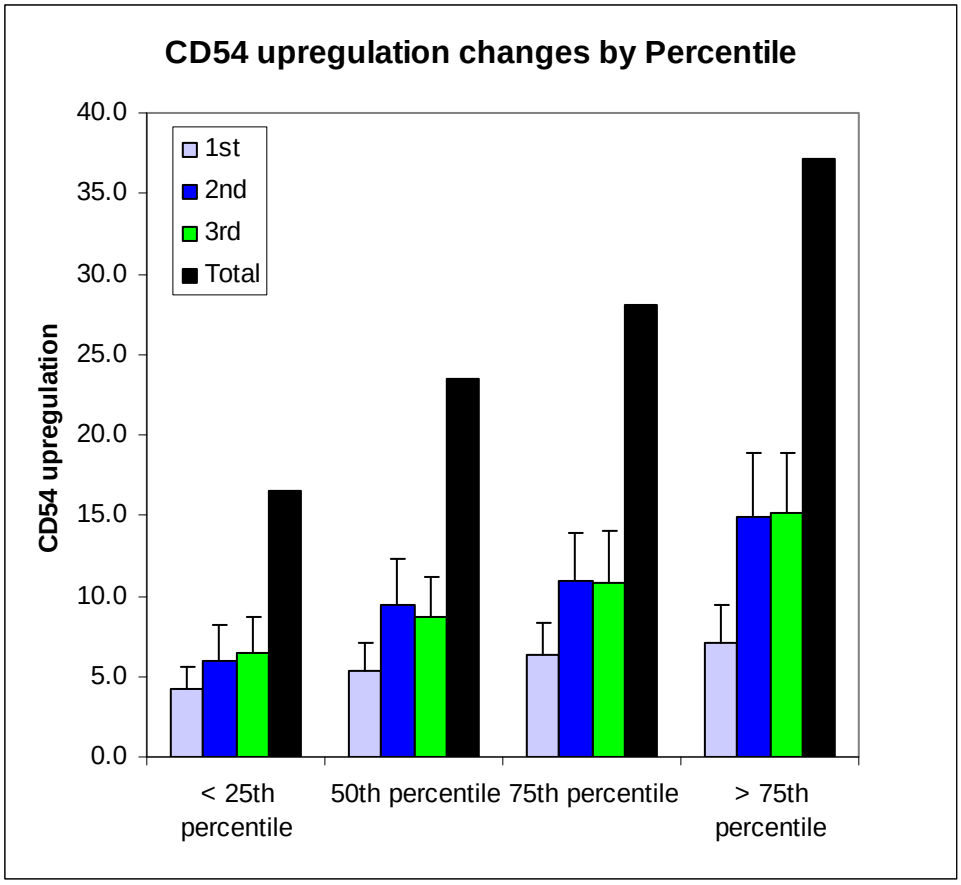


CD54 upregulation was found to be statistically significant ($P = 0.009$) , even after adjustment for baseline prognostic factors (weight, PSA, LDH, number of bone lesions, and localization of disease; $P = 0.022$). The quartile analysis also suggests that patients in the lower quartile have similar level of survival as the placebo group. Whether this is a consequence of 25% of the patients not responding to the therapy, or whether 25% of the lots were not potent is unclear. However, if one performs a quartile analysis on the-b(4)-lots that were included in the BLA once can see some interesting product trends. These trends follow the general observation Dendreon made about the difference between CD54 upregulation in patients that receive sipuleucel-T (infused fresh) versus salvage product (cyropreserved). Those patients who were on the sipuleucel-T treatment arm on average saw a distinct overall level of upregulation on product lots generated after the first infusion. This did not occur in patients that received the salvage product, where all lots were made from cryopreserved cells. This suggest that some kind of immune response may be occurring in patients that received sipuleucel-T. The trend observed for sipuleucel-T holds for all 4 phase III clinical trials. It is interesting, however, that the level seen at week 0 (product lot used for first infusion), was significantly lower than at week 0 in the salvage group, whereas one might expect that week 0 would be the same for both treatments, but higher in the sipuleucel-T treated patients.



As discussed in the product review, this autologous product has very high inherent variability. This variability makes comparisons among groups different. Even so, if one divides the manufactured lots into quartiles based on cumulative CD54 upregulation one sees an interesting trend. In addition to the increased cumulative CD54 upregulation among quartiles, on average production lots among the lowest quartile of lots also had the least level of increased CD54 upregulation in the second and third lots. In other words, even though patient lots are highly variable, the difference in cumulative CD54 upregulation does not appear to be a random event. This analysis was performed by examining all those patients in the four phase III trials (D9901, D9902A, P-11, and D9902B) where 3 infusions had occurred. The main reason why patients in

the lowest quartile achieved a low cumulative CD54 upregulation is because they failed to have much of an increase from the first infusion.



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[b(4)]

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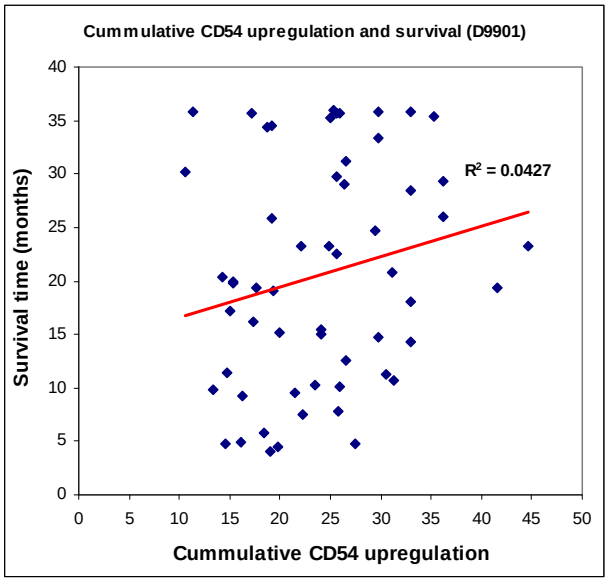
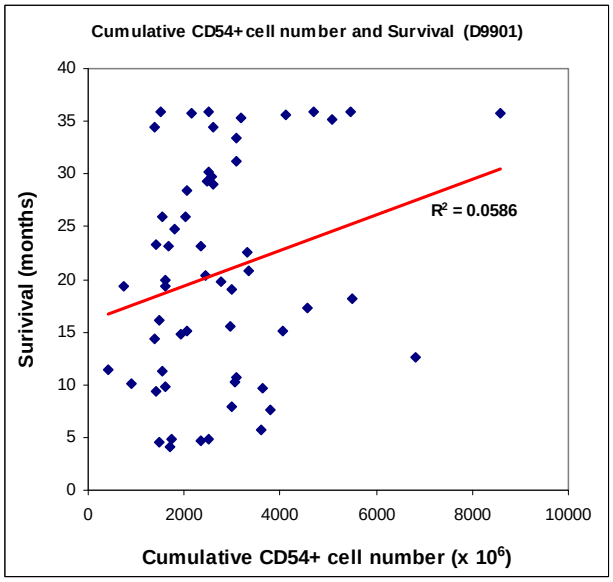
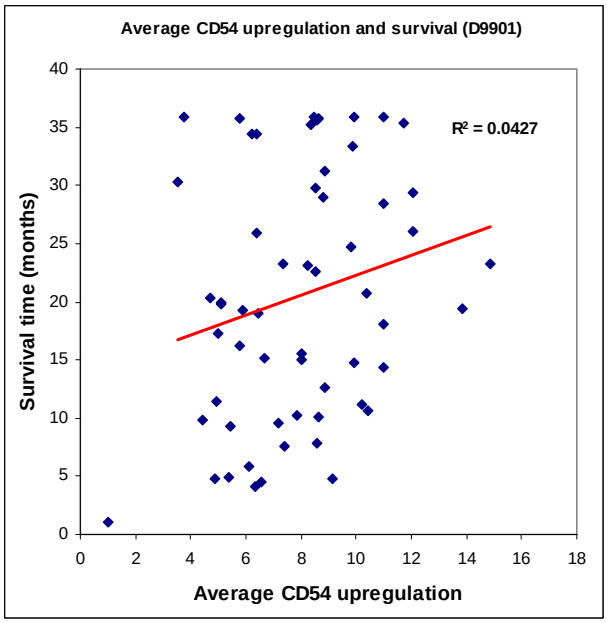
Appendix D: Lot characteristics and correlations

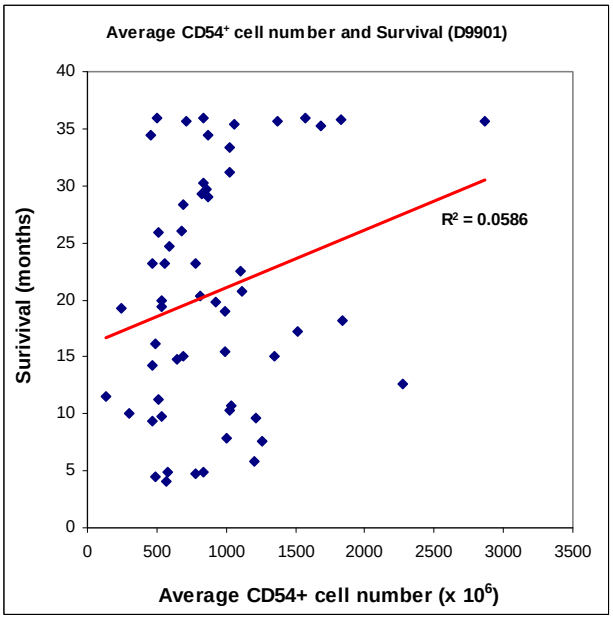
D9901 clinical lots

Dendreon has shown that CD54 upregulation, a potency measurement, correlates with survival. This was based on a combined quartile analysis of D9901 and D9902A. For a discussion of CD54 upregulation among these quartiles see Appendix C. Dendreon also saw (non-statistically significant) trend in $CD54^+$ cell dose on survival. If one examines CD54 upregulation or CD54 cell numbers in the lots used for D9901, however, a poor correlation is seen with survival. The same is true for the average level of expression per patient lot since this number simply represents the cumulative CD54 upregulation divided by 3 infusion lots (only the scale is different). It is unclear why this is the case. It may have to do that this analysis is restricted to just D9901 and not the integrated analysis that Dendreon used for the quartile analysis. Five patients were not included out of the 82 on the treatment arm because they did not receive all 3 infusions.









Correlation in product qualities (D9901, D9902A, P-11)

Sipuleucel-T is a product with high inherent variability. An examination was made of how well some of the more important product qualities correlated with one another. Dendreon partially covered this in the BLA and also used this as the basis for no longer examining the percent -b(4)-- present in the final product. The best relationship is between --b(4)----------. The correlation with b(4) is not surprising considering it makes up about b(4) of the cells in the product. CD54 and -b(4)- do not correlate as well with -b(4)- however -b(4)- and CD54 cell numbers correlate very well, which is important for reasons described above.

[b(4)]

This correlation is not as good of a fit when one plots %CD54 and %-b(4)-. There clear outliers are present. It would be valuable to know if the small number of -b(4)---$CD54^{+}$ lots represent the small circulating DC population present in blood, or are actually T or B cells. As for the small number of lots that are high in -b(4)-, but low in CD54 it is unclear what these cells might be.

[b(4)]

----b(4)----------

[b(4)]

The number of $CD54^+$ cells collected and processed for this therapy might be impacted by either the age of the patient or the weight. As the immune system ages immune cell numbers might decrease. Since the average age of patient for this indication is expected to be varied, it might be relevant to see whether patient age had any effect on the number of $CD54^+$ cells present in the final product. While there is a very slight trend that older patients resulted in lots with fewer cells, this is negligible.

Though no statistical correlation between the number of $CD54^+$ cells and patient survival was seen, current manufacturing criteria state that at least a -b(4)--- leukapheresis volume must

6 Pages determined to be not releasable
b(4)

Appendix G: Potential correlations of product qualities with infusion-related adverse events among D9901

An attempt was made to see if any correlations existed between product properties and adverse events that occurred at the time of infusion. Most patients had mild adverse events associated with this therapy. Common reactions were fever, chills, headache, and aching. More severe reactions included rigors and rarely decrease O_2 saturation or tachycardia. Many patients were treated with Demerol or Benedryl, and in some cases pre-medicated.

Not all patients had a reaction. 27 patients had no infusion-related reactions, and most of those had 3 infusions. 54 patients had some kind of reaction, with many of them being mild. Those that did have a more serious reaction did not have a reaction for every infusion. There did not seem to be a pattern to the reactions- infusion related reactions sometimes occurred for the first infusion, sometimes for the second or third.

Considering the large differences lot to lot, it is possible that some of these events could be associated with either dose or cell composition. As highlighted elsewhere cell dose can vary by as much as b(4) fold patient to patient, and the percent of "contaminating" T cells or B cells in the product can range considerably.

Cell dose. No correlation could be found between cell dose and infusion reaction, either in terms of total b(4) infused or the number of $CD54^+$ cells present in the lot. For example, some patients had a reaction after receiving a small dose, but had no reaction for the next infusion where they received a much larger dose. Some patients received many times the dose of other patients and still had no reaction. To perform the analysis production lots were grouped according to those patients where there was no reaction; or those with a reaction to at least one of the infusions, but not to the lots in the subset; or to those lots where an infusion-related reaction was seen. No significant difference was seen between those lots associated with an infusion reaction verses the other two groups where there was not an association.

Cell composition. Clinical trial D9901 was conducted at a time when Dendreon was still recording the percent --b(4)---------- present in the final product. If one examines the same-b(4)- subgroups of production lots, no obvious or statistically significant relationship can be seen with the percentage of these cells and the occurrence of infusion-related reactions. However, there is a slight trend that those lots with -b(4)- cell levels (%-b(4)-) might have some association. Given the high variability of the product and the variability of the reaction, to examine further such a correlation would take much more data. Perhaps this is something that could be followed in the commercial product as a post-marketing agreement. This would require that Dendreon re-instate measuring these markers in the final product.

2 Pages determined to be not releasable
b(4)

Appendix H: Immune monitoring

Dendreon performed a limited evaluation of the immune response to sipuleucel-T. Immune monitoring was not performed in all trials. For example, no studies were done in D9902A, and so far it does not appear that any analysis has been performed in D9902B, --b(4)---------- Dendreon has stated that one limitation is in getting patient samples sent back to them for analysis. Another problem has been in consistency in the T cell assays. The thought is that if more samples could be assayed at the same time, then consistency may improve.

Even when immune monitoring was performed in a trial, it was not routinely performed and the number of patients examined is somewhat small. Also, some assays appear to have only been done once. It is not clear that Dendreon has put a high priority on measuring the immune response in patients in their trials. Considering that there appears to be very little tumor antigen-specific immune response in the vaccinated patients, one would think that this would be a high priority. Finally, it is difficult to fully interpret the data presented because few details were included on how the studies were performed and figure legends were not provided.

Below is a table copied from the BLA summarizing immune measures performed in their clinical trials.

Table 1 Clinical Pharmacology Studies

Protocol Title (status)	Population	Treatment	Analyses
ACT 9610 (completed)	Advanced AIPC	Phase 1 (N = 12) APC8015: Weeks 0, 4, 8, and 24 Phase 2 (N = 19) APC8015: Weeks 0, 4, 8, and 24	Proliferation; ELISA
ACT 9702 (completed)	Advanced AIPC	Phase 1 (N = 13) APC8015: Weeks 0, 4 and PA2024: Weeks 8, 12, 16 Phase 2 (N = 21) APC8015: Weeks 0, 2 and PA2024: Weeks 4, 8, 12	Proliferation; ELISA
D9901 (completed)	Asymptomatic, metastatic, AIPC	Phase 3 (N = 49) APC8015: Weeks 0, 2, and 4	Proliferation; ELISA
P-11 (ongoing)	Non-metastatic prostate cancer in patients with a rising PSA following radical prostatectomy	Phase 3 (N = 16) APC8015: Weeks 0,2, and 4, and booster at disease progression	Proliferation; ELISPOT

Abbreviations: AIPC = androgen independent prostate cancer; SC = subcutaneous delivery

Dendreon concluded from these studies that "The pharmacodynamic evaluation of sipuleucel-T in men with AIPC participating in Phase I, Phase II, and Phase III trials has focused on the cellular and humoral immune response to the target antigen, PA2024. The data demonstrate that men who receive sipuleucel-T mount a significant immune response against PA2024. Early studies of dosing regimens and routes of administration helped define the dose for the Phase III studies. Immune monitoring data from Phase III studies were exploratory, but did demonstrate the in vivo activity of sipuleucel-T."

Changes in cell composition.

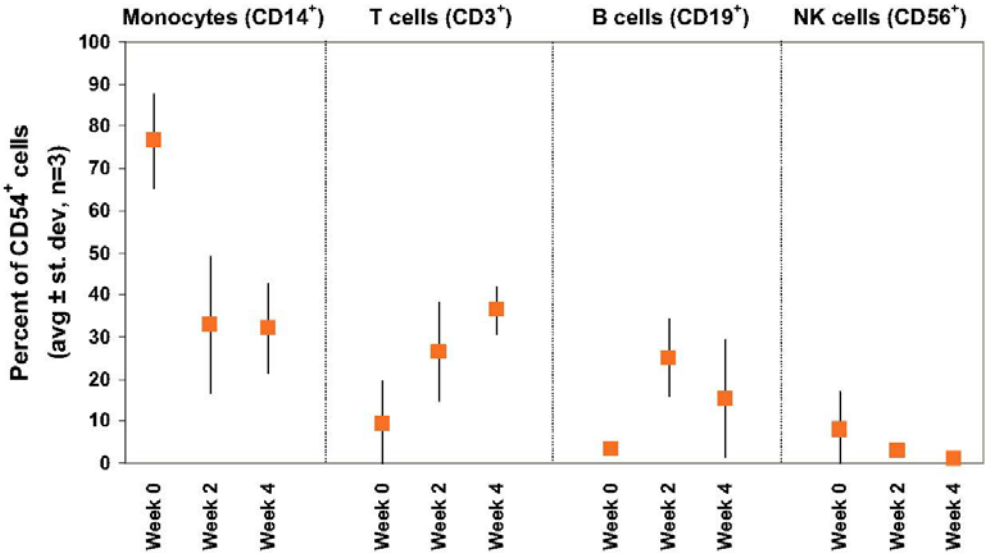
----b(4)---------- ----------

------b(4)---------- ----------

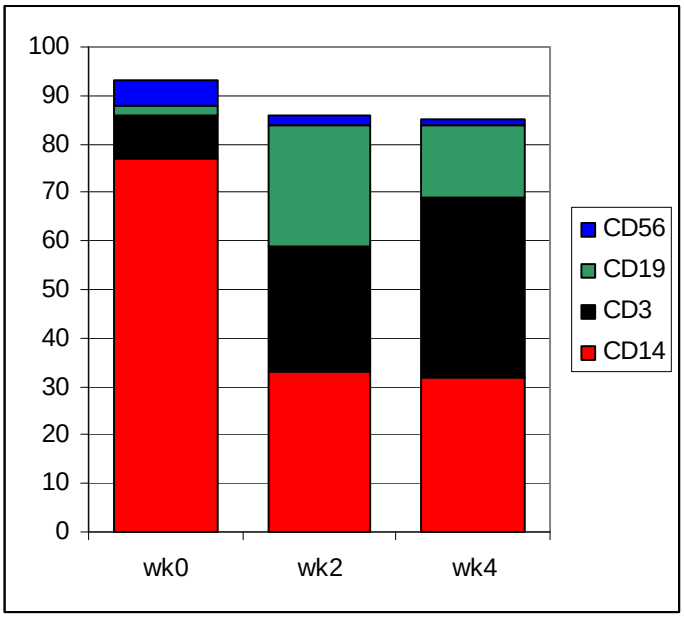
--b(4)-- ----------

----------, which would be the APC, even before activation. For the analysis depicted below they are talking about all $CD54^+$ cells. As you can see monocytes (APC) decrease in peripheral blood and $CD3^+$ T cells

Figure 36 **Composition of the CD54$^+$ Cell Population in Sipuleucel-T over Successive Treatments**



go up. Interestingly, the error bars don't seem all that big for this set of patients. What this means is unclear, but it may be an indication of an immune response, or a non-specific consequence of the therapy. Plotted another way, the data looks as follows:



Since in order for this therapy to be effective the activated monocytes need to leave the blood stream and go to the site of the tumor and lymph nodes, the reduction in monocyte number might be a reflection of this process, although that is probably a vast over-interpretation of the data. What the increase in CD3$^+$ cells means is unclear. It would be interesting for Dendreon to follow

up this observation with a much larger set of patients. However, considering Dendreon is no longer monitoring these markers, at least in the production lots, it is unclear whether they intend to continue.

T cell stimulation

Unlike the antigen-pulsed dendritic cells, the PAP-GM-CSF fusion protein did not elicit T-cell responses to PAP in preclinical studies. In one of their clinical trials that involved subcutaneous injections of the fusion protein they observed that the injections did not stimulate T-cell or antibody responses. Results from phase I and phase II studies (Small et al., 2000. Journal of Clinical Oncology, 18(23):2894-3093) did, however, show that some patients have strong responses to PA2024 fusion protein when treated with sipuleucel-T. This indicates that while PA2024 was unable to generate much of an immune response, monocytes activated withPA2024 did result in T cell proliferation to at least PA2024. When they examined cytokine secretion by ELISPOT they saw that the patients' pretreatment T cells did not secrete either IFNγ or IL-4 in response to PA2024. However, T cells collected after treatment with Provenge secreted IFNγ but not IL-4 in response to PA2024, indicating a Th1-type response. This data was not shown unfortunately. In addition, ELISPOT assays of cytokine secretion by single lymphocytes showed that the frequency of cells secreting IFNγ in response to PA2024 increased from undetectable (< $1/10^6$ cells) to 1/5763 cells and 1/5181 cells for the two patients who were studied.

In the phase I/II ACT 9610 trial some PAP-specific immune response was measured, as summarized in this table from the case study report. However, when results were presented for this trial in section 2.7.2, Dendreon listed the T cell stimulation index against human PAP as -b(4)-. It is not clear why there is this discrepancy, however Dendreon did not include the data in their briefing package to the advisory committee.

Table 5: Summary of T cell Proliferation Data for all Phase 1 and Phase 2 Subjects (N = 31)[a]

	PA2024	Human PAP	GM-CSF	--b(4)--------	-b(4)---
Subjects with pre-existing responses at Week 0	8/31 (26%)	4/31 (13%)	10/30 (33%)	-b(4)---- ---------	-b(4)---- ---------
Subjects with a ≥ 5-fold increase in SI following treatment	30/31 (97%)	13/31 (42%)	15/28 (54%)	-b(4)---- ---------	-b(4)---- ---------
Subjects with a ≥ 10-fold increase in SI following treatment	28/31 (90%)	8/31 (26%)	9/28 (32%)	-b(4)---- ---------	--b(4)----
Subjects with a ≥ 15-fold increase in SI following treatment	25/31 (81%)	4/31 (13%)	6/28 (21%)	-b(4)---- ---------	--b(4)----

Source: Tables 14.2.1, 14.2.2, 14.2.3, and

14.2.4

[a]Response data was not obtained for all subjects. SI = stimulation index. Stimulation index was calculated as the median count per minute (CPM) at a given antigen concentration divided by the median CPM for the control. The data presented reflect the maximum increase in SI that occurred at any follow-up time-point, and at any in vitro antigen concentration, tested during the study.

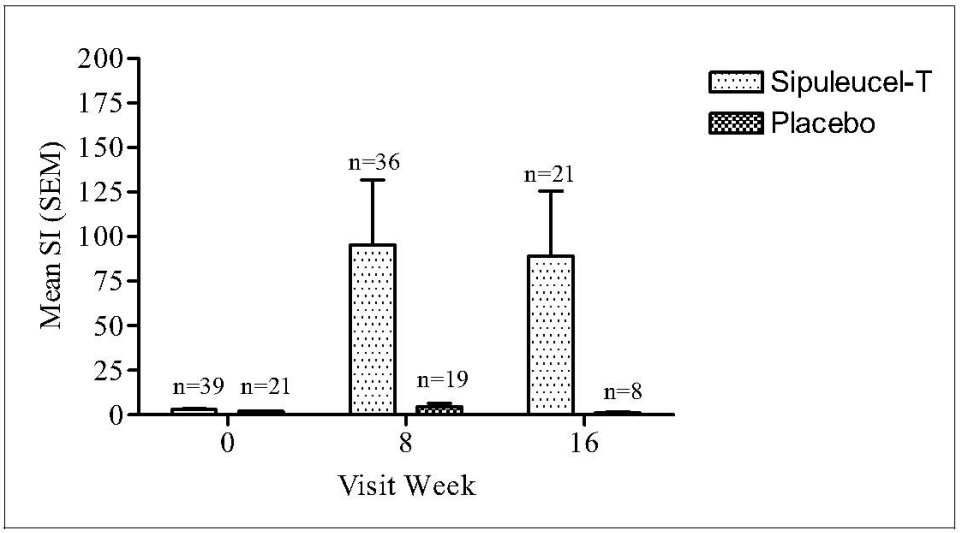
--b(4)---------- ----------

[b(4)]

--b(4)---- ----------

[b(4)]

In D9901 they saw a substantial response to sipuleucel-T (PA2024). The stimulation index for the response is remarkably high for a peripheral blood T cell assay. Here again, they summarize the data in a table which seems to indicate a much weaker response. In another evaluation of T cell response the level of stimulation was much smaller. Using a standard --b(4)----------
---------- assay they found an average stimulation index of less than -b(4) before subtracting the placebo response. No response was seen to PAP, only PA2024. It is not clear how they are calculating the median of the geometric mean., but that might explain the difference in the data presentations.



D9901 data

Table 21 **Analyses of Stimulation Index Ratios Using Geometric Means and 50 µg/mL of Antigen, Week 0 to Weeks 8 and 16**

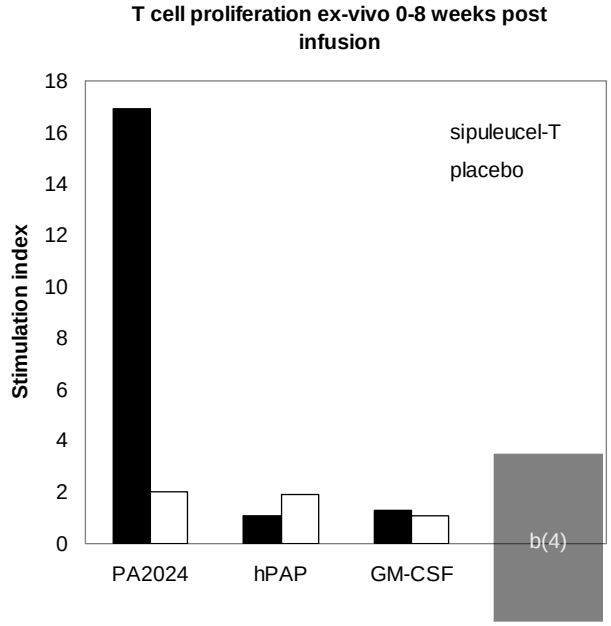
Antigen	APC8015	APC-Placebo	p-value
	Median of the Geometric Mean		
Week 0 to Week 8	**n = 31**	**n = 16**	
PA2024	16.91	1.99	0.0004
Human PAP	1.07	1.90	0.2238
GM-CSF	1.31	1.09	0.7306
b(4)			
Week 0 to Week 16	**n = 14**	**n = 8**	
PA2024	13.22	0.91	0.0001
Human PAP[a]	0.99	0.40	0.0890
GM-CSF	0.76	0.37	0.3650
Junction Peptide[a]	1.47	0.55	0.2685

[a] For human PAP at Week 16 in the APC8015 group, N = 13

b(4) 50 µg/mL b(4)

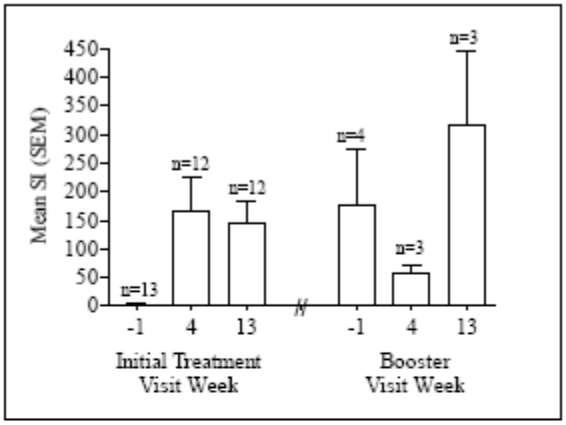
Source: Post-Text Table 14.2.28 (09 MAY 2006)

This same data is presented graphically here.

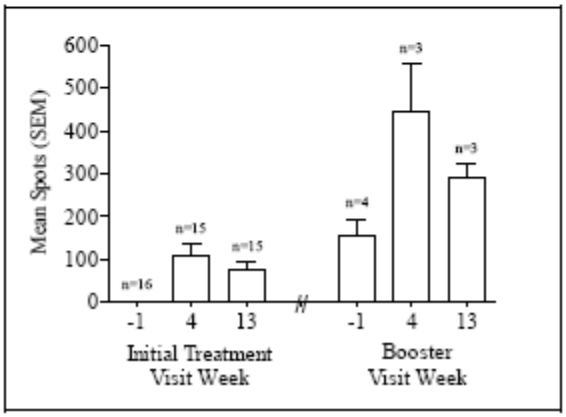


A similar high level of response was seen in the P-11 trial where some patients got a 4th booster infusion. The stimulation index rises dramatically after 4 weeks and remains high. A IFNγ ELISPOT also showed a significant response that seem to be much higher after the 4th booster vaccination.

P-11: Stimulation Index of PA2024 (10 µg/mL) Over Time for Subjects Treated with APC8015



P-11: IFNγ ELISPOT of PA2024 (10 µg/mL) Over Time for Subjects Treated with APC8015



The fact that they are able to get a response to PA2024, but consistently not to PAP tumor antigen is troubling. Dendreon should try and determine what epitopes these T cells are responding to. They have, or at least did have, --b(4)---------- that were used to characterize the ----b(4)----------. These could be used to evaluate at least some of the patient responses. Of course, it does not seem like they use these same peptides in their --b(4)---------- assays as a positive control, so perhaps they no longer exist.

Ab response. Dendreon also examined antibody titers to PA2024, seminal PAP, and GM-CSF in some patients. The way they presented the data is a little weird because they don't actually discuss the titer, but they did see a response. The antibody response was more limited compared to the T cell response, but was consistent across trials. Response to these same antigens was negligible in the placebo patients.

Table 31 N (%) of a ≥ 16-fold Antibody Response Following Treatment, by Study

Antigen	ACT 9610	ACT 9702	Study 1 (Sipuleucel-T)	Study 1 (Placebo)
PA2024	20 (67)	25 (86)	27 (90)	1 (6)
Seminal PAP	9 (30)	2 (7)	2 (7)	0 (0)
GM-CSF	14 (48)	18 (62)	14 (47)	0 (0)

In a early phase clinical trial where they were injecting GM-CSF separately they did see a little anti-GM-CSF response by ELISA, but no anti-PAP response. The response to PA2024 was nearly 10 fold higher after treatment, but the response to GM-CSF was more than 2000 fold higher. From the 2004 publication (Burch, et al. 2004, The Prostate, 60:197-204):

TABLE III. Antibody Titers in Patient Sera Before (Week 0) and After Treatment (Week 16)

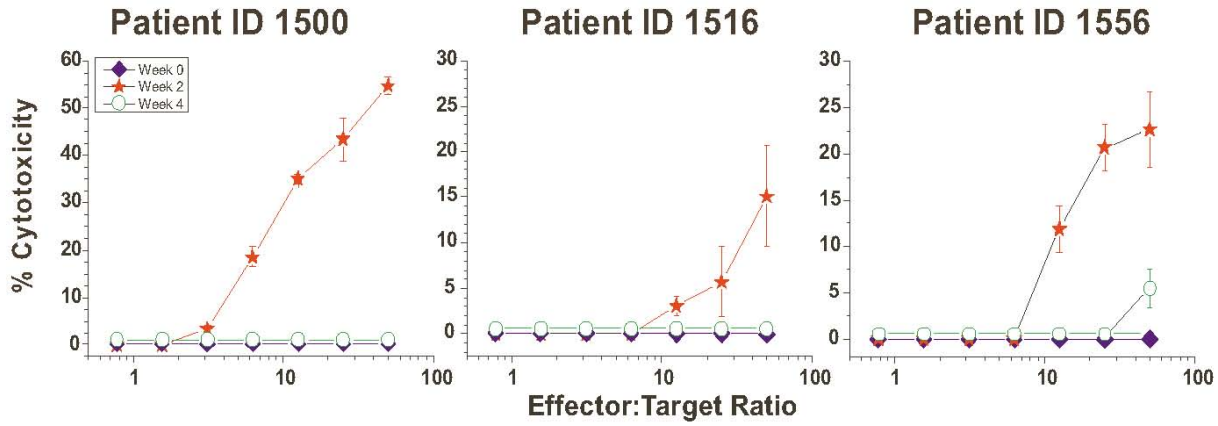
Antigen	Number of evaluable patients	Antibody titer, mean (standard deviation)	Antibody titer, median (range)
Week 0			
PAP	15	1.3 (3.51)	0 (0–10)
PA2024	15	1,370 (5,290)	0 (0–20,480)[a]
GM-CSF	15	2.0 (5.6)	0 (0–20)
Week 16			
PAP	10	2.0 (4.2)	0 (0–10)
PA2024	10	12,810 (8,610)	16,640 (2,560–20,480)
GM-CSF	10	4,790 (8,310)	1,280 (0–20,480)

[a]These values stem from the one patient who displayed PA2024-reactive antibodies before treatment. In all other patients titers were 10 or less.

The authors of the study did not comment on the strong anti-GM-CSF response. It is a little puzzling why such a response was seen in this study, but the in the other 3 trials only half of the patients had a response. Perhaps that half had a very significant strong responses.

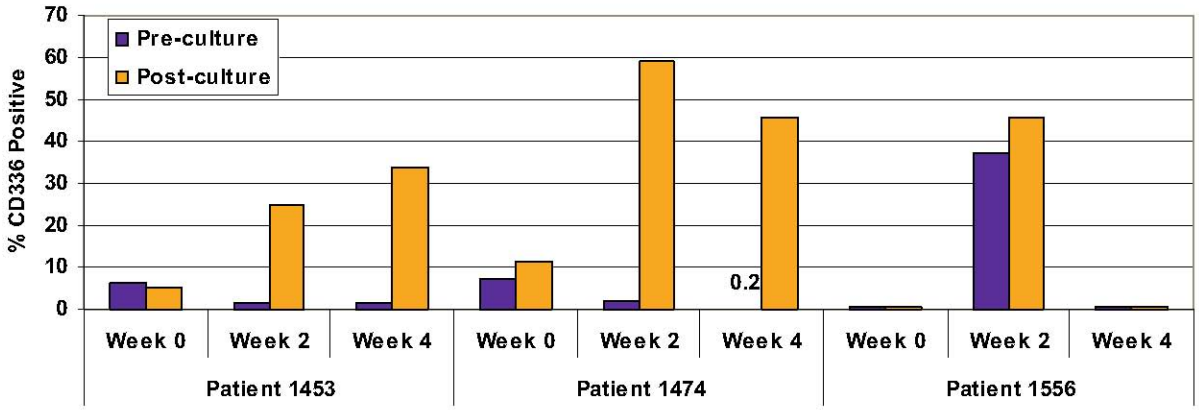
NK cell activity. Data from one experiment shows that in the 3 patients they examined they got a very decent NK response ex vivo, but only at week 2 (after infusion). No response at all at week 0 or 4.

Figure 38 NK Lytic Activity at Treatment Weeks 0, 2 and 4 (n = 3)



Dendreon also performed an analysis using CD336 as a NK cell marker and examining changes in the percent of NK activity. CD336 (Nkp46) is one of three Natural Cytotoxicity Receptors expressed on NK cells. In the 3 patients examined the percent of $CD336^{+}$ NK cells present in an ex vivo assay increase after week 0. This is supportive evidence that the infused product is eliciting some kind of immune response in vivo.

Figure 37 NK Cell Activation during Ex Vivo Culture at Treatment Weeks 0, 2 and 4 (n = 3)



Summary of immune monitoring. It is difficult to draw conclusions from the immune monitoring data for several reasons. For some assays only a few patients were examined, and in cases where a reasonable number of patients was examined, no response against PAP was seen. Only PA2024 seems to consistently generate an antigen specific response. It is puzzling how the stimulation index data is presented. If the peripheral blood T cell response is really as high as they are suggesting in some of their graphs, then that would represent a very strong response to PA2024. It is not clear why if they can get that level of response why they do not see much more of a response to PAP. Dendreon intends to perform some --b(4)---------- assays and maybe --b(4)---------- for the ongoing D9902B study, but as yet have not performed any of the assays.

Hopefully, the results will be clearer in those studies. During a telecon with Dendreon to discuss some of these figures that were included in Dendreon's advisory committee briefing package it was asked if they had any evidence of a specific response to human PAP. They stated that no they do not yet have any evidence.

Cytokine production ex vivo. Dendreon examined ex-vivo cytokine production for sipuleucel-T product incubated for 4 weeks. Cytokines were measured in the supernates. The greatest level of cytokine secreted into the medium was -b(4)- by far. Not surprising fro this mixture of cells was the presence of a variety of cytokines, including --b(4)-------- cytokines.

1 Page determined to be not releasable
b(4)

Appendix I. Lot release specifications

	Lot Release Parameter	Early IND specification	IND Specification	Revised IND Specification	BLA Specification
Identity	--b(4)----------		--b(4)---	--b(4)---	--b(4)---
	--b(4)-----		--b(4)---	--b(4)---	--b(4)---
Purity	--b(4)----------		-----b(4)----------	----b(4)----------	--b(4)---
	--b(4)------	--b(4)---	--b(4)---	--b(4)---	--b(4)---
	--b(4)----------	--b(4)---	----b(4)----------	--b(4)----------	--b(4)---
	--b(4)----------				--b(4)---
	--b(4)---	--b(4)---	------b(4)----------	--b(4)---	--b(4)---
	--b(4)---	--b(4)---	-----b(4)----------	--b(4)---	--b(4)---
	--b(4)---	--b(4)---	-----b(4)----------	--b(4)---	--b(4)---
	--b(4)--- ----------		------b(4)----------	-----b(4)----------	--b(4)---
Potency	CD54 Fold Upregulation	--b(4)---	--b(4)---	--b(4)---	--b(4)---
	Number of CD54 cells	--b(4)---	--b(4)---	--b(4)---	--b(4)---
Safety	--b(4)---				
	--b(4)---	--b(4)---	----b(4)----------	--b(4)----------	--b(4)---
	--b(4)----------	----b(4)----------	-----b(4)----------	--b(4)----------	--b(4)---
	--b(4)----------			--b(4)----------	-b(4)----------
	Final Product Sterility				
	-----b(4)----------	----b(4)----------	----b(4)----------	--b(4)----------	--b(4)---
	-----b(4)----------			--b(4)----------	--b(4)----------
	Endotoxin	--b(4)---	--b(4)---	--b(4)---	--b(4)---
	Gram Stain	------b(4)----------	-----b(4)----------	--b(4)----------	--b(4)----------

[a] Results available post-infusion.

[b] Results are available, but not part of lot release specs

-b(4)----- method is used in place of CFR method